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# Association between Global Brain Volume and the Rate of Cognitive Change in Elderly Humans without Dementia

## A 2-Year Follow-Up Study

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### Key Words

Questionable dementia · Brain volume · Hippocampus · Corpus callosum · Longitudinal study · Neuroimaging

### Abstract

Patients with mild cognitive deficits experience different types of evolution. They are at increased risk of developing dementia, but they have also a chance of remaining stable in cognition or of improving. We investigated whether global brain volume, callosal size and hippocampal size are associated with the rate of cognitive change in elderly without dementia. Volumetric MR images were recorded from 39 controls and 35 patients with questionable dementia who were followed up longitudinally for a mean of 2.3 years. The outcome measure was the annual change in the test score in the Structured Interview for the Diagnosis of Alzheimer's Dementia and Multi-Infarct Dementia, which includes all items of the Mini-Mental State Examination. Global brain volume, grey matter volume and white matter volume were the only significant independent predictors of the rate of cognitive change.

### Introduction

With advancing age, the cognitive abilities of many people decline to some degree [1]. Those mild cognitive deficits are unspecific and heterogeneous regarding aetiology and course [2]. Often, they do not progress or even improve. However, in old age the probability increases that cognitive deficits are due to Alzheimer's disease (AD) or another illness which leads to the manifestation of a dementia syndrome [3, 4].

Clinically, the different types cannot be accurately differentiated or predicted. Accurate biomarkers of the most frequent dementing illnesses (in particular AD) are still lacking [5]. Moreover, there is no established consensus on diagnostic criteria and clinical labels [6–9]. One method for defining mild cognitive deficits involves the use of dementia severity rating scales, which all include preclinical forms of dementia [9]. So-called 'questionable dementia' (QD) refers to a score of 0.5 in the Clinical Dementia Rating (CDR) [10].

There is evidence that volumetric brain measures can support the early diagnosis of dementing illnesses. Several longitudinal neuroimaging studies in individuals without dementia showed that the volume of temporal

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areas and particularly the hippocampus is associated with the subsequent development of dementia (see recent reviews) [11–13]. However, this association is only moderate and seems not satisfactory for clinical purposes and the assessment of isolated cases [12]. Whether other volumetric parameters such as global brain volume or callosal size have any predictive value, has rarely been investigated. First longitudinal findings regarding the global brain volume are encouraging [14–18].

In almost all neuroimaging studies, the question has been neglected whether volumetric measures are independent predictors. Only a minority of neuroimaging studies reported findings in direct comparison with neuropsychological tests [12]. However, neuropsychological tests, particularly measures of memory, are associated with the development of dementia [19]. In patients with AD, impaired cognition is supposed to be caused by neuropathological changes and by the resulting atrophy [20]. Because of this link, neuropsychological and volumetric measures may yield corresponding diagnostic information. For clinical purposes, it might be redundant or ineffective to measure both.

This prospective longitudinal study investigates whether global brain volume, hippocampal volume and callosal size are independent predictors of a future change in cognitive function in elderly subjects without dementia (individuals with normal cognition and individuals with QD). The hypothesis is that smaller volumes are associated with accelerated cognitive decline.

## Methods

### *Participants*

The longitudinal study was initiated in August 1997. 74 participants without dementia (age range 73–87 years) were enrolled. Most participants ( $n = 68$ ) were consecutively recruited for this study from the Leipzig Longitudinal Study of the Aged (LEILA75+) [21]. To ensure that participants represented a cognitive continuum, they were recruited according to Mini-Mental State Examination (MMSE) strata [22]. They represented approximately 10% of the non-demented LEILA75+ sample in the same age range. Six additional non-demented participants were consecutively recruited from the local memory clinic, the inclusion criteria were a CDR score of 0.5 (see below) and age between 75 and 85 years. All of them had subjective memory complaints. 30% of the sample recruited by LEILA75+ had subjective memory complaints. Written informed consent was obtained from all participants after complete description of the study. All participants were clinically investigated as described previously [22]. Presence of signs of depression were rated using the Montgomery-Asberg Depression Rating Scale (MADRS) [23]. Cognitive skills were assessed based on the test performance part of the Structured Interview for the Diagnosis of

Dementia of the Alzheimer-type, Multi-infarct Dementia and Dementias of other aetiologies according to ICD-10 and DSM-III-R (SIDAM) [24]. This neuropsychological screening instrument consists of 55 items, including all 30 items of the MMSE [25]. It allows the investigation of the following domains: orientation, immediate recall, delayed recall, long-term memory, intellectual abilities, verbal abilities/calculation, visuospatial function and aphasia/apraxia. In cases with cognitive deficits, a relative was interviewed. The degree of cognitive impairment was rated using the CDR, which comprises the scales memory, orientation, judgement and problem solving, community affairs, home and hobbies as well as personal care [10]. The CDR was scored independently of the psychometric assessment. According to the CDR rates, participants were classified in two groups: 39 cognitively normal controls (CDR = 0) and 35 patients with QD (CDR = 0.5). Participants with QD typically suffered from mild forgetfulness, they were fully oriented, had no or slight impairment in social functions and did not meet ICD-10 dementia criteria. None of the participants had a history of a major psychiatric illness or Parkinson's disease based on medical history. Mild depressive symptoms did not lead to exclusion from the study.

### *Magnetic Resonance Imaging*

Participants were investigated by a 1.5-tesla tomograph (Siemens Vision) with a volumetric  $T_1$ -weighted MPRAGE sequence (TR 11.4 ms, TE 4.4 ms, 128 slices, orientation transverse, matrix  $256 \times 256$ , voxel size  $0.9 \times 0.9 \times 1.5$  mm) and by a  $T_2$ -weighted protocol (TR 5,016 ms; TE 132 ms; 19 slices, thickness 5 mm; orientation transverse, 1-mm gap; matrix  $357 \times 512$ , voxel size  $0.5 \times 0.5 \times 6$  mm). Data sets were analysed using the BRIAN software package [26]. The volumetric data sets were aligned with the stereotactic co-ordinate system [27], using the anterior and posterior commissure as reference points and scaled to an isotropic voxel resolution of 1 mm.

From the whole three-dimensional data set grey and white matter, internal and external cisterns (cerebrospinal fluid compartments, CSF) were automatically determined using a boundary-guided region-growing procedure [28]. Intracranial volume (ICV) was defined as the sum of total brain volume and CSF volume. Six cross sections of the hippocampus were segmented manually in the coronal plane on both sides. Hippocampal measures started behind the amygdala at the slice in which the area of the hippocampal head appeared maximal and were continued posteriorly at 3-mm intervals [22]. The corpus callosum was outlined manually in the sagittal slice best representing the midsagittal plane (little or absent grey matter and a visible septum pellucidum) [29]. Manual outlining techniques have previously been shown to have a high inter-rater reliability. For hippocampal size, intraclass correlation was 0.996 [22]; the average difference between the hippocampal measures of 2 raters did not differ significantly from 0. For the corpus callosum, intraclass correlation was 0.918 [30], the average inter-rater difference also did not differ significantly from 0.

Based on the  $t_2$ -weighted images, white matter changes were assessed. Using a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), the degree of periventricular white matter hyperintensities (PVH), deep white matter hyperintensities (DWMH) and dilated perivascular spaces (DPS) was rated. Intrarater experiments (by H.W.) demonstrated a high reliability with kappa values of 0.88 for DPS, 0.92 for DWMH and 0.95 for PVH [31].

### Follow-Up

Participants were re-examined after a mean of 2.3 years (SD 0.62, range 1–4 years). Again participants were investigated clinically and cognitive skills were assessed using SIDAM. Changes in cognitive functions were determined by subtracting the baseline SIDAM score (SISCO) from the follow-up SISCO and then this difference was divided by the follow-up interval: annual change in SISCO = (follow-up SISCO – baseline SISCO)/follow-up interval. Accordingly, the annual change in MMSE score was computed.

Three groups were formed according to the outcome: (1) decline (participant declined at least 1.5 points/year); (2) stability (participant changed less than 1.5 points/year); (3) improvement (participant improved at least 1.5 points/year). To find an appropriate cutoff, this study relied on the 1-standard deviation (SD) interval of the annual change in SISCO, as it proved to be normally distributed. The cutoff at 1.5 points/year marks quite accurately the limits of 1 SD. It includes 69% of the sample (see 'Results'). Longitudinal studies of the 'normal' change in SISCO are lacking. However, the MMSE was found to decline by 0.9 points on average in men and by 1.0 point in women during 5 years and by 1.3 points over 28 months [32, 33].

### Statistical Analysis

All statistical computations were performed using SPSS for Windows (version 8.0.0). The significance level was set to be 0.05 for all analyses. Baseline characteristics were compared using U test or Kruskal-Wallis-H. Normal distribution of the annual change in SISCO and the annual change in MMSE was tested using Kolmogorov-Smirnov test. Differences between the control group and the QD group in the average annual change in SISCO were tested using U test, variance homogeneity was tested using F test by Levene. To make volumes of brain structures comparable – which are different in size – and to make men and women comparable, measures were z-transformed separately for each gender. Repeated stepwise backward linear regression analyses were performed to predict the annual change in SISCO. Firstly, only clinical and psychometric variables were included (model 1). Secondly, z-transformed volumetric brain measures were additionally included; namely in those combinations in which they were only moderately associated with each other ( $r < 0.7$ ) to avoid collinearity (models 2–4). The interdependence of the predictor variables was examined by correlation analyses, the alpha level was adjusted for multiple testing by Bonferroni-Holm. In all regression analyses and correlation analyses one extreme case has been excluded to produce normal distribution. Because the exclusion of an outlier can distort the results, all findings were double-checked. For that purpose the outlier was included and the outcome variable was logarithmically transformed. Results were essentially the same. Group differences in volumetric brain measures were compared by analyses of variance (ANOVA) with group as a factor and ICV as a covariate. The alpha level was again adjusted for multiple testing by Bonferroni-Holm.

## Results

Table 1 summarises the baseline characteristics of the control group and of the QD group. Both groups differed significantly from each other in the baseline MMSE ( $U =$

**Table 1.** Baseline characteristics of the control group and the QD group ( $n = 74$ )

	Controls ( $n = 39$ )	QD ( $n = 35$ )
Female	22 (56.4%)	26 (74.3%)
Age, years	$79.4 \pm 2.9$	$79.9 \pm 3.3$
Education, years <sup>1</sup>	$12.5 \pm 2.3$	$10.8 \pm 1.9$
MMSE <sup>1</sup>	$28.9 \pm 1.1$	$26.2 \pm 1.8$
SISCO <sup>1</sup>	$51.1 \pm 2.8$	$45.1 \pm 3.5$
MADRS median	3	3
MADRS 25th–75th percentile	0–6	2–10
Left hippocampus <sup>2</sup>	$0.38 \pm 0.93$	$-0.42 \pm 0.90$
Right hippocampus <sup>2</sup>	$0.37 \pm 0.84$	$-0.41 \pm 1.00$
Corpus callosum	$0.09 \pm 1.01$	$-0.10 \pm 0.98$
ICV	$0.15 \pm 0.98$	$-0.17 \pm 1.00$
Brain volume	$0.13 \pm 1.07$	$-0.15 \pm 0.89$
White matter volume	$0.13 \pm 1.11$	$-0.15 \pm 0.83$
Grey matter volume	$0.12 \pm 1.06$	$-0.13 \pm 0.91$
Internal CSF volume	$-0.12 \pm 0.56$	$0.13 \pm 1.32$
External CSF volume	$0.16 \pm 1.01$	$-0.18 \pm 0.95$

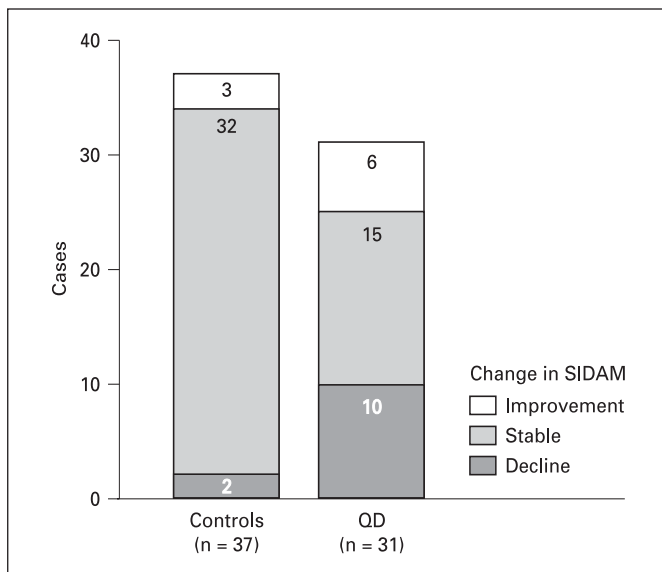
Data are given as mean  $\pm$  SD (except for MADRS). All brain measures have been z-transformed. SISCO = Score of the test performance part of the Structured Interview for the Diagnosis of Alzheimer's Dementia and Multi-Infarct Dementia.

<sup>1</sup>U test showed a significant difference between the groups.

<sup>2</sup>ANOVA showed a significant difference between the groups.

104.5,  $n = 74$ ,  $p < 0.001$ ), the baseline SISCO ( $U = 91.0$ ,  $n = 74$ ,  $p < 0.001$ ) and years of education ( $U = 403.0$ ,  $n = 74$ ,  $p = 0.002$ ). The difference in MMSE and SISCO was still significant when the influence of education on test performance was controlled for by means of regression analysis. Groups did not differ in age or in length of the follow-up interval. Signs of depression were slightly more frequent in the QD group, but the difference was not significant. ANOVA with group as a factor and ICV as a covariate showed that control participants had significantly larger hippocampal volumes than participants with QD: z-transformed left hippocampus ( $F_{1,71} = 11.7$ ,  $p < 0.01$ ), z-transformed right hippocampus ( $F_{1,71} = 10.8$ ,  $p < 0.01$ ). The control group and the QD group did not differ significantly in any other volume. The majority of control participants and of QD participants had white matter changes. Chi-square test showed no group difference. Out of 74 participants, mild to moderate DPS were found in 70% of the cases, severe DPS in 20%. Mild to moderate PVH was present in 80% of the participants, severe PVH in 16%. Mild to moderate DWMH was seen in 70% of the participants, severe DWMH in 10%.





**Fig. 1.** The annual change in the test performance in SIDAM in individuals with normal cognition and patients with questionable dementia (QD) followed up over 2.3 years (n = 68). A change of 1.5 points per year was used as a cutoff for the definition of the three outcome groups.

**Table 2.** Average annual change in MMSE and in SISCO (n = 68)

	Controls (n = 37)	QD (n = 31)
Change in MMSE	0.0 ± 0.5	-0.6 ± 1.9
Change in SISCO	0.2 ± 1.2	-0.9 ± 3.3

Data are given as mean ± SD.

**Table 3.** Significant predictors of annual change in SISCO (n = 67)

Model	Standardised beta	p	Corrected R <sup>2</sup>
1 baseline CDR sum score	-0.72	0.000	0.23
baseline SIDAM score	-0.63	0.000	
age	-0.24	0.033	
2 <sup>a</sup> + grey matter volume	0.25	0.021	0.28
3 <sup>a</sup> + total brain volume	0.24	0.032	0.28
4 <sup>a, b</sup> + white matter volume	0.20	0.084	0.26

<sup>a</sup> Models 2–4 also include the CDR sum score, SIDAM score and age. Their coefficients are not reported to avoid redundancies.

<sup>b</sup> If age is excluded, white matter volume is a significant predictor with p = 0.025.

Out of 74 participants at baseline, 68 participants were followed up (37 controls, 31 QD). Six participants were lost because of death (n = 3), inability to contact (n = 1) or refusal (n = 2). U test showed that participants who dropped out did not differ from participants who were followed up in age, years of education, MMSE or SISCO.

Four women (all had initially QD) were diagnosed as having dementia at follow-up. According to ICD-10 criteria, 3 had mild dementia in AD, 2 of them were diagnosed as atypical or mixed type. One participant with a severe dementia syndrome was shielded by her relatives. According to the medical records, her dementia syndrome was caused by multiple strokes, i.e. vascular dementia. She had experienced an extreme change in test performance in SIDAM (-14 points/year).

At follow-up, CDR scoring was done in 55 cases (31 controls, 25 QD). In the remaining 13 probands CDR scoring would not have been reliable, because interviews with relatives were not possible. All 31 controls, who were again assessed with the CDR, received again a CDR global score of 0. Out of 25 probands with QD at baseline, 5 improved to a CDR global score of 0, 15 received again a CDR score of 0.5 and 4 a CDR score ≥ 1. Because of the missing values and the resulting lack of statistical power, we decided not to add the CDR as an outcome variable.

Out of the 68 participants that were followed, most participants (69%) experienced a small change in SISCO (<1.5 points/year). Thirteen percent improved more than 1.5 points/year, 18% declined more than 1.5 points/year. The control group proved to be significantly more steady in cognitive function than the QD group (fig. 1). Only 14% of the control group changed more than 1.5 points/year, whereas 52% of the QD group did. Accordingly, the degree of variance of the annual change in SISCO (table 2) was significantly smaller in the control group (F = 11.5, p = 0.001). There was no significant difference in the average change in MMSE and in the average change in SISCO between the control group and the QD group.

Coefficients of the regression models which significantly explained the annual change in SISCO are listed in table 3. Older age, a higher CDR sum score and surprisingly also a higher baseline SISCO were significantly associated with decline in cognitive function (model 1). Gender as well as years of education lacked association to the annual change in SISCO. Of all brain measures, only the z-transformed total brain volume, grey matter and white matter volume (models 2–4) were significant

**Table 4.** Pearson's correlation coefficients between volumetric brain measures (n = 67)

	Left HC	Right HC	CC	ICV	Total brain	Internal CSF	External CSF	White matter	Grey matter
Left HC	1								
Right HC	0.79 <sup>a</sup>	1							
CC	0.15	0.10	1						
ICV	0.36 <sup>a</sup>	0.37 <sup>a</sup>	0.47 <sup>a</sup>	1					
Total brain	0.40 <sup>a</sup>	0.38 <sup>a</sup>	0.48 <sup>a</sup>	0.81 <sup>a</sup>	1				
Internal CSF	0.05	0.04	-0.20	0.22	0.16	1			
External CSF	0.10	0.16	0.26	0.56 <sup>a</sup>	0.03	-0.22	1		
White matter	0.31	0.31	0.54 <sup>a</sup>	0.67 <sup>a</sup>	0.92 <sup>a</sup>	0.12	-0.06	1	
Grey matter	0.45 <sup>a</sup>	0.40 <sup>a</sup>	0.36 <sup>a</sup>	0.82 <sup>a</sup>	0.93 <sup>a</sup>	0.19	0.11	0.73 <sup>a</sup>	1

All brain measures have been z-transformed. HC = Hippocampus; CC = corpus callosum. Because multiple analyses were computed, the alpha level was adjusted by means of Bonferroni-Holm.

<sup>a</sup> Correlation is significant at the adjusted alpha level (one-tailed).

**Table 5.** Baseline characteristics of the three outcome groups (n = 68)

	Decline (n = 12)	Stability (n = 47)	Improvement (n = 9)
Initial QD	10 (83.3%)	15 (31.9%)	6 (66.7%)
Female	11 (91.7%)	28 (59.6%)	5 (55.6%)
Age, years <sup>1</sup>	81.6 ± 3.4	79.4 ± 3.1	78.6 ± 2.2
MMSE <sup>1</sup>	26.5 ± 2.2	28.3 ± 1.2	25.4 ± 3.0
SISCO <sup>1</sup>	45.8 ± 5.1	49.7 ± 3.1	43.4 ± 5.1
Education, years	10.5 ± 2.1	11.8 ± 2.3	12.6 ± 2.3
MADRS median	3	2	3
MADRS 25th–75th percentile	1–7	1–7	0–5
Left hippocampus	-0.35 ± 1.09	0.22 ± 0.98	-0.36 ± 0.41
Right hippocampus	-0.20 ± 1.26	0.11 ± 0.92	-0.14 ± 0.68
Corpus callosum	-0.27 ± 1.17	0.04 ± 0.99	0.26 ± 0.78
ICV	-0.26 ± 1.26	0.02 ± 0.98	0.51 ± 0.78
Brain volume	-0.30 ± 1.15	0.14 ± 1.04	0.21 ± 0.47
White matter volume	-0.30 ± 1.13	0.13 ± 1.02	0.05 ± 0.64
Grey matter volume	-0.26 ± 1.10	0.12 ± 1.03	0.32 ± 0.41
Internal CSF volume	0.14 ± 1.40	0.08 ± 0.97	-0.33 ± 0.61
External CSF volume	-0.08 ± 1.23	-0.15 ± 0.82	0.60 ± 1.16

Data are given as mean ± SD. All brain measures have been z-transformed.

<sup>1</sup>Kruskal-Wallis H testing showed a significant difference between the three groups at the 0.05 level.

independent predictors and improved the proportion of explained variance achieved by model 1.

There was some interdependence between the predictor variables. Naturally, the z-transformed volumetric measurements of several brain compartments correlated strongly with each other (table 4). It was therefore unreasonable to include all brain measures simultaneously in

one regression model to predict the annual change in SISCO. Moreover, the baseline SISCO correlated significantly with the CDR sum score ( $r = -0.66$ ,  $n = 67$ ,  $p < 0.001$ ), the left hippocampal volume ( $r = 0.39$ ,  $n = 67$ ,  $p < 0.001$ ) and the right hippocampal volume ( $r = 0.33$ ,  $n = 67$ ,  $p < 0.001$ ). Analogous, the CDR sum score correlated significantly with the left hippocampal volume ( $r = -0.41$ ,  $n =$

67,  $p < 0.001$ ) and the right hippocampal volume ( $r = -0.38$ ,  $n = 67$ ,  $p < 0.001$ ) as well as with the years of education ( $r = -0.33$ ,  $n = 67$ ,  $p < 0.001$ ).

Baseline characteristics of the three outcome groups decline, stability, and improvement are summarised in table 5. Participants who declined as well as participants who improved both had significantly lower baseline MMSE and baseline SISCO than stable participants and did not differ from each other. This corresponds to the fact that most decliners and most improvers had been diagnosed as QD at baseline. Improvers were significantly younger and completed more years of education than decliners. All brain structures as well as the external CSF were larger in the improvement group than in the decline group, except the left hippocampus. The internal CSF was largest in the decline group. However, ANOVA showed no significant group effect in any brain structure. Chi-square test showed that the three outcome groups did not differ in the degree of white matter changes. Moreover, they did not differ in the length of the follow-up interval or in the degree of signs of depression.

## Discussion

In the current study we investigated whether global brain volume, callosal size and hippocampal size are independently associated with the rate of cognitive change in elderly subjects without dementia, i.e. individuals with normal cognition and individuals with QD.

39 cognitively normal participants and 35 participants with QD were included. The QD group can be assumed to be heterogeneous regarding the aetiology of cognitive impairment. According to present knowledge, it is likely that most QD patients suffered from very mild AD [34, 35]. In other participants with QD, cognitive impairment might have been related to age and to vascular changes. Accordingly, the participants experienced different courses of cognitive change. Most participants remained almost steady in cognitive function and changed not more than 1.5 points/year in SISCO. There was a small variance in the outcome variable. Parallel to this steadiness, the association between the predictor variables and the outcome was moderate. The maximal proportion of explained variance of the annual change in SISCO was 28%.

The proportion of participants who experienced cognitive decline during the study corresponds to previous reports. 11.4% of the QD group ( $n = 4$ ) developed a dementia syndrome. Petersen et al. [36] reported conversion rates to dementia between 10 and 15%, other reviews re-

ported conversion rates up to 25% [9, 37]. Considering the sample characteristics and the outcome, the results can be interpreted in the light of knowledge about AD.

Among all brain measures, only global brain volume, grey matter volume and white matter volume were significant independent predictors of the annual change in SISCO. One explanation for this superiority might be that a reduction of global brain volume is linked with a more advanced stage of AD than atrophic changes of midtemporal areas, which occur at earlier stages. The neuropathological studies by Braak and Braak [38] showed that neurofibrillary tangles – one feature of AD – evolve in six typical stages and that they spread out in non-limbic cortical regions at later stages of the disease. This ‘neocortical stage’ is related to the development of dementia, although there is evidence that some patients develop dementia without involvement of the neocortex [20, 39, 40]. Memory deficits that are already present before the onset of a dementia syndrome seem to be related to the spreading of neurofibrillary tangles into midtemporal (limbic) areas [20]. The hippocampus is affected in this so-called ‘limbic stage’.

Other explanations for the superiority of global brain volume measures are their ‘non-specificity’ regarding the location of brain tissue loss and the so-called ‘reserve hypothesis’. Because global brain volume is sensitive to atrophic changes independently of their location, it is able to indicate the general state of the brain. This is important because recently evidence was provided showing that cognitive decline in mild cognitive impairment is associated with global brain damage [41]. Hippocampal volume and callosal size are more specific measures and indicate only changes in localised regions. The reserve hypothesis implies that a larger premorbid brain size protects against the effects of ageing and AD. Total brain, grey and white matter volume represent to some degree the premorbid brain size. The theory is discussed controversially. Both indication for its validity was found [42, 43] and negative results have been reported [44].

In conclusion, the results of this study suggest that global measures of brain volume are associated with further cognitive change in patients with QD and in individuals with normal cognition. This is in line with previous longitudinal neuroimaging studies. Fox et al. [14] found increased rates of cerebral atrophy in patients subsequently developing dementia. Fischl et al. [15] found that patients with stable QD differed in all ventricular substructures from patients with progressive QD. Analogous to our study, Forstl et al. [16] showed that the rate of change in MMSE is associated to the degree of brain

atrophy in patients with age-associated memory impairment and with AD. Mungas et al. [17] reported that atrophy of the cortical grey matter predicted a cognitive decline in individuals without dementia and with AD. Marquis et al. [18] found reduced total brain volume in healthy participants who subsequently converted to a CDR score of 0.5 or more. Also cross-sectional studies reported reduced global volume parameters in patients with mild cognitive impairment [45, 46].

By way of contrast, our results contradict previous longitudinal studies of the predictive value of hippocampal volume. Reviews of a great number of recent publications indicate that in individuals with mild cognitive deficits initial hippocampal volume is moderately associated with the future development of AD [11, 12]. The difference to this study might be due to a difference in outcome variables. Most of previous studies have aimed to predict dementia in AD, while this study aimed to predict the rate of change in a neuropsychological test. The clinical relevance of this outcome measure is emphasised by the finding that accelerated cognitive decline is a feature of dementing illnesses, though there is great variability in the rate of change in patients with AD [47]. In 8 out of 12 cases with accelerated cognitive decline no dementia syndrome had been diagnosed at the follow-up visit. Consequently, the level of cognitive function was on average higher in this group than in groups consisting exclusively of patients with dementia. In principle, SISCO mirrored hippocampal function, as both measures correlated significantly with each other at baseline. In conclusion, this study indicates that hippocampal atrophy is not necessarily associated with the rate of cognitive change in elderly subjects without dementia.

As to measures of the corpus callosum, they seem unsuitable to predict future cognitive change in elderly without dementia. To the best of our knowledge there is only one previous longitudinal study. Hampel et al. [48] showed that AD patients have significantly greater rates of corpus callosum atrophy than controls. Two previous cross-sectional studies showed a non-significant reduction of callosal size in patients with QD and incipient dementia compared to controls [49, 30]. The result has been replicated on an enlarged sample now.

A surprising result of this study was that a high baseline SISCO was associated with decline, while a low baseline SISCO was associated with improvement. This may be due to the ceiling effect. Participants with high test scores cannot improve. Other causes might be practice and regression to the mean on a repeated measurement. However, all participants that converted to dementia al-

ready had a SISCO in the lowest quartile of the whole sample at baseline. The opposite effects might have led to the weak degree of association between baseline SISCO and outcome.

Comparison of the outcome groups 'decline', 'stability' and 'improvement' will be discussed only shortly. The results correspond to the above-discussed findings because the definition of the outcome groups was based on the annual change in SISCO. However, the differences between the groups in the brain volume measures were small and not significant. The lack of significance might be due to the use of a cutoff for the definition of the outcome groups. The cutoff was modelled on the normal distribution (which was present) but nevertheless arbitrary. In principle, this study provides evidence that improvement is a possible outcome of QD. This type of course is mostly neglected in imaging studies. According to present knowledge, 11–25% of patients with mild cognitive deficits improve in cognitive function, and improvement seems to be stable [50–52].

This study used the rate of cognitive change as outcome measure. This approach is unusual in neuroimaging studies (see above). Therefore the properties shall be pointed out that seem decisive. The outcome variable directly refers to the time course of the actual cognitive change. It allows to differentiate fast and slow progression, to describe improvement and changes within one diagnostic category. It might not only be relevant whether a patient develops a dementia syndrome. It might be also important at which rate changes occur. This question can only be answered when the outcome variable includes information about time.

*Limits of the Study.* The study was carried out within a 2-year period, which is a relatively short interval. It may be that some participants will develop dementia in the future. The definition of the outcome variable – the annual rate of cognitive change – was assumed to be independent of the length of the follow-up interval. This is not necessarily the case, as cognitive decline might develop non-linearly. Moreover the statistic power of this study was limited. Particularly the comparison between participants who declined and improved was based on only 21 participants and is thus prone to statistical type II error. Because of the small sample size, it was impossible to determine measures of diagnostic accuracy and to analyse the data in relation to the development of a dementia syndrome and to the change in the CDR global score.



## Conclusions

Measures of global brain volume are independently associated with the rate of cognitive change in elderly subjects without dementia. However, they seem to add only little information to clinical and psychometric information.

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